Epithelial-mesenchymal transition and drug resistance in breast cancer (Review)

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Abstract. Breast cancer is the leading cause of cancer death in women worldwide. Insensitivity of tumor cells to drug therapies is an essential reason arousing such high mortality. Epithelial-mesenchymal transition (EMT) is defined by the loss of epithelial characteristics and the acquisition of a mesenchymal phenotype. It is well known that EMT plays an important role in breast cancer progression. Recently, mounting evidence has demonstrated involvement of EMT in antagonizing chemotherapy in breast cancer. Here, we discuss the biological significance and clinical implications of these findings, with an emphasis on novel approaches that effectively target EMT to increase the efficacy of anticancer therapies.

Contents

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide, accounting for ~23% of the total new cancer cases and 14% of the total cancer deaths (1). It is well known that breast cancer is a heterogeneous disease that can be classified by microscopic appearance and molecular profiles such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) which correlate with diverse clinical outcomes and responses to treatment. Systemic treatment for breast cancer, including conventional cytotoxic therapy (paclitaxe, doxorubicine, cyclophosphamide, fluorouracil, cis-platinum), endocrine treatment (tamoxifen, fulvestrant, letrozole, anastrozole), and targeted agents such as trastuzumab, plays an essential role in reducing mortality rate and prolonging survival time in patients with breast cancer (2,3). However, resistance to therapeutic agents remains a consistent obstacle in terms of treatment success, while the underlying mechanism of drug resistance remains enigmatic (4,5).

Epithelial-mesenchymal transition (EMT) is a biologic process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal cells. A growing body of literature supports that EMT is closely linked to the progression of breast cancer, which includes enhanced migratory and invasive capacity, and elevated stemness of cancer cells (6,7). Now, emerging evidence suggests that EMT is also involved in treatment resistance in breast cancer (8,9). This review presents the events that involve the impact of EMT on drug resistance in breast cancer, helping understand the generation of treatment resistance and seek potential approaches to reverse the process.

2. Drug resistance in breast cancer

In breast cancer treatment, conventional cytotoxic agents used alone or in combination weaken and destroy cancer cells in the body. However, resistance to chemotherapy is a major hurdle in the management of breast cancer. Some patients exhibit intrinsic resistance to chemotherapy, while other patients, although initially sensitive to chemotherapy, eventually develop acquired resistance, even after combination therapy. At present, it is well accepted that the mechanisms of chemoresistance may mainly contain decreasing uptake of

water-soluble drugs, various changes in cells that affect the capacity of cytotoxic drugs to kill cells and increasing energy-dependent efflux of hydrophobic drugs that can easily enter the cells by diffusion through the plasma membrane (10). Moreover, topoisomerase poisons, altered expression of drug-metabolizing enzymes and drug-conjugate export pumps, suppression of apoptotic pathways and host-tumor-drug interactions also contribute to chemoresistance (11). Among these, the most significant is the increased efflux of hydrophobic drugs which are regulated by a family of energy-dependent transporters, known as ATP-binding cassette (ABC) transporters including P-glycoprotein (P-gp, also known as ABCB1 or MDR1), multidrug resistance protein (MRP) 1-7, lung resistance-related protein (LRP) and breast cancer resistance protein (BCRP) (12).

Tamoxifen (TAM) is the usual endocrine (anti-estrogen) therapy inducing objective response or disease stabilization in breast cancer patients with ER^+ tumors. The pharmacologic action of tamoxifen is that it binds to the estrogen receptor and induces dimerization and DNA binding to finally inactivate it (13). Nevertheless, about half of ER^+ patients with advanced disease and nearly all patients with metastatic disease fail to respond to first-line TAM treatment. Approximately 40% of patients receiving TAM as adjuvant therapy experience tumor relapse and die from their disease, and a third of women treated with TAM for 5 years develop recurrent disease within 15 years (14). TAM resistance might arise as a consequence of loss of expression or function of ERα, including autophosphorylation, modulation by activation of transmembrane tyrosine kinase receptors and interaction between downstream signal transduction pathways (15).

Trastuzumab (herceptin), a humanized, recombinant monoclonal antibody that selectively binds with high affinity to the extracellular domain of HER2, has been proved to exert antitumor effects in cancer models and patients with HER2-amplified breast cancer. The addition of trastuzumab to adjuvant chemotherapy can impressively reduce the recurrence rate (16). However, some patients with HER2-overexpressing breast cancer do not respond to trastuzumab therapy. There is only 26% response rate in women diagnosed with HER2-positive metastatic breast cancer and treated with trastuzumab as a single first-line agent. That is, >70% of HER2-overexpressing metastatic breast carcinomas display a resistance to trastuzumab (17). The mechanisms underlying the resistance phenotype are not well understood. Increased production of insulin-like growth factor, dysregulation of p27, overexpression of epidermal growth factor receptor (EGFR) with activation of the Akt pathway and decreased PTEN function may contribute to this process (18).

3. The potential mechanism of EMT

EMT refers to a complex molecular and cellular program by which epithelial cells shed their differentiated characteristics, including cell-cell adhesion, planar/apical-basal polarity, and lack of motility, and instead acquire mesenchymal features. It has been described as the transition taking place in epithelial cancer cells, which may lead to cancer invasion, resistance to anoikis and systemic cancer cell dissemination (19). During the acquisition of EMT characteristics, cells undergo actin cytoskeleton reorganization, decrease in the expression of proteins that promote cell-cell contact such as E-cadherin and occludin, and gain in the expression of mesenchymal markers such as vimentin, fibronectin and N-cadherin, as well as increased activity of matrix metalloproteinases (MMPs) like MMP-2, MMP-3 and MMP-9, which are associated with an invasive phenotype (20). The tumor microenvironment comprised of extracellular matrix, cells, and soluble factors plays a critical role in EMT induction and further in tumor metastasis (21,22). Several kinds of stromal cell subtypes, such as macrophages and fibroblasts, contribute to tumor progression through induction of EMT (23,24). EMT can also be triggered by adverse conditions such as hypoxia and a diverse set of extracellular stimuli including tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), epithelial growth factor family member (EGF), fibroblast growth factor (FGF), insulin growth factor (IGF), platelet derived growth factor (PDGF), and components of the extracellular matrix such as collagen and hyaluronic acid (21). Signal transduction pathways including Wnt, Notch, nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) and phosphatidyl inositol 3-kinase (PI3K) pathways can coordinate EMT programs. Different stimuli induce a multitude of signal pathways that converge on several EMT-inducing transcriptional factors including Snail, Slug, Twist, Zeb1, Zeb2. All of the factors are capable of repressing E-cadherin directly or indirectly when overexpressed in cultured epithelial cells (25) (Fig. 1).

4. EMT transcriptional factors and drug resistance in breast cancer

It is well established that Snail family proteins (Snail and Slug) are the key regulatory elements of EMT along with the control of expression of many genes. Snail is involved in the EMT that not only takes place concomitantly with the acquisition of invasive properties in tumors, but also has been related to other cancer hallmarks such as the gain of unlimited replication potential, a greater resistance to apoptosis and even the evasion of immunosurveillance (26). Vega *et al* found that Snail attenuated the cell cycle and conferred resistance to cell death induced by the withdrawal of survival factors and pro-apoptotic signals (27). In another study, aberrant expression of Snail or Slug in breast adenocarcinoma cells was observed to protect against apoptosis induced by genotoxic stress, which might be associated with direct transcriptional repression of genes taking part in many aspects of programmed cell death (28). Chen *et al* revealed that MCF-7 breast cancer cells transfected with eukaryotic expression vector pCDNA3.1-Snail showed EMT with BCRP-mediated multidrug resistance (29). Similarly, it was reported that overexpression of Snail accelerated adriamycin induction of multidrug resistance through increasing the expression of P-gp (30). In paclitaxel, docetaxel, or doxorubicin resistant MCF-7 cell lines, Slug expression was upregulated and ER was downregulated, resulting in the repression of E-cadherin and occludin, and elevation of N-cadherin and vimentin (31,32). MCF-7 cells with ER deprivation were unresponsive to addition of estradiol and TAM and acquired the EMT state (33). It was shown that decrease in the estrogen dependency of breast cancer cells was accompanied by an increased expression and activity

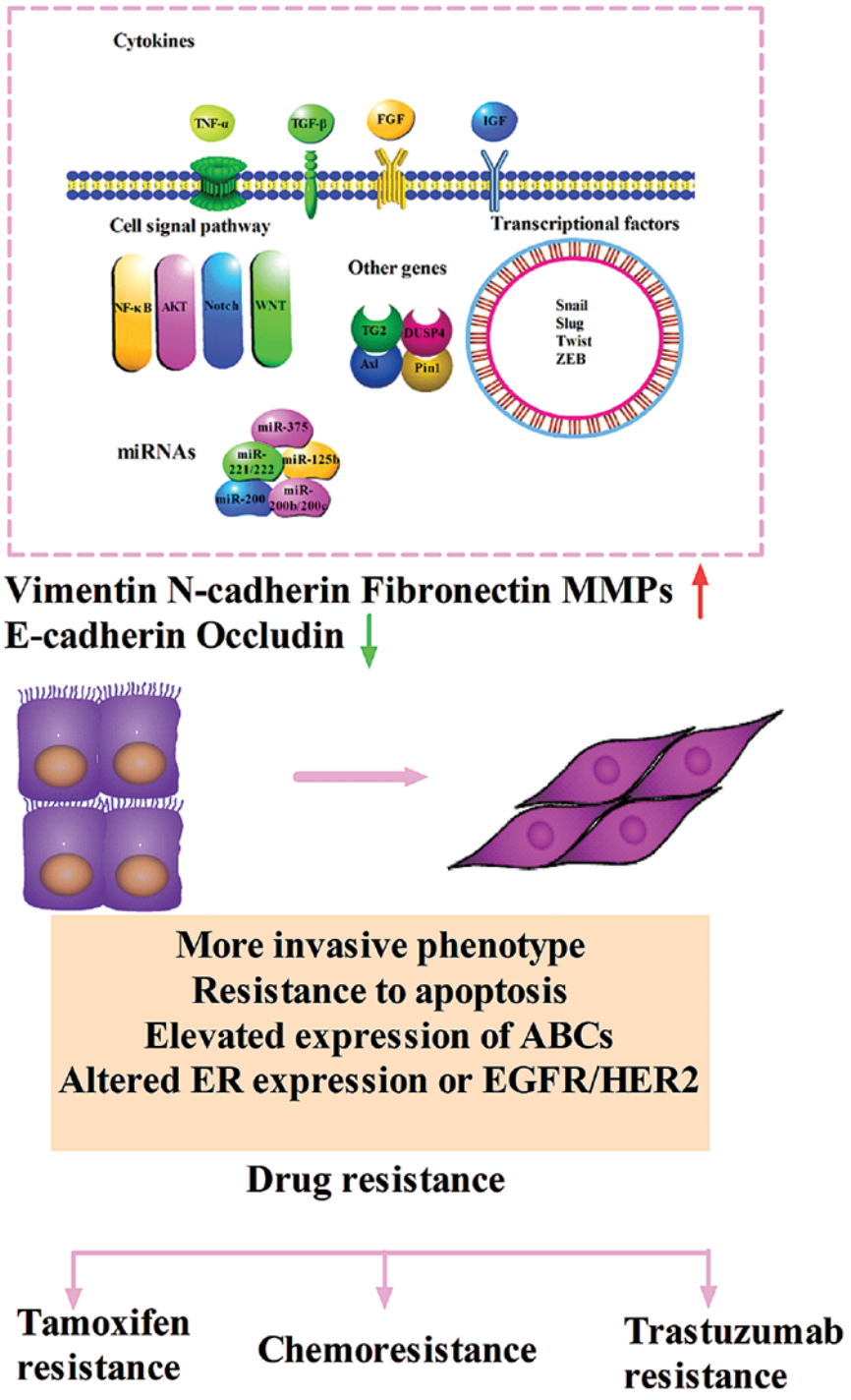

Figure 1. Brief representation of the role of transcriptional factors, cytokines, cell signal pathways, miRNAs and some other genes in EMT and drug resistance in breast cancer.

of Snail, and demonstrated the involvement of Snail in the negative regulation of ER (34). Further findings demonstrated that Snail could repress ER-α expression by direct interaction with regulatory DNA sequences at the ESR1 locus in breast cancer cell lines (35). In addition, many ERα-negative lines which were also E-cadherin-negative (e.g., MDA-MB-468 and MDA-MB-231) exhibited high Slug expression. It is indicated that ligand-activated ERα formed a transcriptional inhibitory complex comprised of nuclear receptor co-repressor (N-CoR) and histone deacetylase 1 (HDAC1) which bonds to the Slug promoter and directly suppresses Slug, which is one of the critical members in Slug-E-cadherin-EMT pathway (36). Highly invasive breast cancer cell lines expressed elevated levels of Twist, which upregulated the transcription of Akt-2 to promote cell survival and resistance to paclitaxel (37). Li *et al* proved that adriamycin induced EMT and apoptosis in MCF-7 cells, while only cells undergoing EMT displayed multidrug resistance. Twist1 suppression prevented the drug-induced P-gp expression, concomitant with partial reduction in resistance to paclitaxel, vincristine and bleomycin (38). It seems that EMT induction simultaneously upregulates the expression of several ABC transporters, which lead to mutidrug resistance in human

breast cancer cells. There were binding sites for several EMT transcription factors (Snail, Slug, Twist and FOXC2) in 16 ABC transporters, while CHIP analysis further revealed that Twist directly bound to E-boxes in the promoter region of ABCC4 and ABCC5 in MCF-7 cells transfected with Twist (39).

5. EMT-related cytokines and drug resistance in breast cancer

TGF-β is one of the most potent and better-studied inducers of EMT, acts through serine-threonine kinase receptors to phosphorylate the cytoplasmic Smads which activates E-cadherin repressors of the Snail family. A recent study indicated that adverse activation of TGF-β pathway by chemotherapeutics in the breast cancer cells or elevated TGF-β levels in tumor microenvironment might lead to EMT and generation of cancer stem cells, resulting in the resistance to chemotherapy (40). The evidence found cis-platinum treatment of MDA-MB-231 breast cancer cells increased both TGF-β mRNA levels and the secretion of active TGF-β, which enhanced growth arrest that facilitated repair of damage, thus rendering these cells resistant to cis-platinum killing (41). In the report of López-Díaz *et al*, TGF-β was shown protected cells from DoxR, 5-fluorouracil and paclitaxel-induced cell death specifically though Smad 4-mediated complex (42). Moreover, TGF-β pretreatment was able to attenuate the TAM cytotoxic effect and decrease the apoptosis ratio in breast cancer (43). It was reported that TGF-β increased ErbB/PI3K activation in BT474 and SKBR3 cells, and desensitized the cells to trastuzumab-mediated growth inhibition (44). TNF-α is another inflammatory cytokine linked to both EMT and drug resistance. MCF-7TN-R cells which were generated by prolonged and progressive exposure of MCF-7 cells to TNF-α underwent progressive EMT changes, and represented a model of transition to a multidrug resistant and increased tumorigenic phenotype. In addition, some growth factors which induce EMT may also take part in acquired resistance by various patterns. IGF-1 was proposed to transmit signals via both the PI3K and MAPK pathways, then resulted in the extracellular activation of MMPs which were capable of promoting latent TGF-β1-induced EMT, further rescued breast cancer cells from chemotherapy-induced cell death (45,46). It was also demonstrated that IGF-1 stimulated phosphorylation of HER-2 exclusively in the trastuzumab resistant cells. Antibody-mediated blockade of insulin growth factor repector (IGF-1R) disrupts IGF-1R interaction with HER-2 and restores trastuzumab sensitivity (47). FGF expression was found as a stronger predictor of paclitaxel resistance, compared to P-gp, p53, or Bcl-2 in patients with breast cancer (48). With the interaction with ER-activated pathways, FGF receptor-mediated signaling drives autonomous growth which would be refractory to TAM therapy (49). Regarding the induction of FGF on EMT, these results suggested that EMT might be involved in the FGF-mediated chemoresistance process.

6. EMT-related signal pathways and drug resistance in breast cancer

Many signaling pathways which have significant regulating effects on EMT are closely involved in drug resistance. Genomic Region Enrichment was performed to find increased secretase activity which may account for an increased Notch signaling in endocrine resistant breast cancer cells (50). PF-03084014 which inhibits Notch signaling by reducing Notch intracellular domain (NICD) and Notch target genes Hes-1 and c-Myc in both cells and tumors prominently enhanced the antitumor activity of docetaxel in MDA-MB-231 xenograft model through suppressing expression of survivin and myeloid cell leukemia sequence 1 (MCL1), reducing ABCB1 and ABCC2, upregulating BIM and reversing the EMT phenotype (51). Notch may be an important target in trastuzumab-resistant, HER-2$^+$ breast cancer. Growth of trastuzumab-resistant cells was completely inhibited by combining trastuzumab plus Notch-1 siRNA (52). The NF-κB pathway is emerging as an essential regulator of EMT in cancer cell lines acting through the induction of Snail transcription and protein stabilization. Constitutively active NF-κB was also discovered to play a key role in resistance to death-inducing stimuli, including chemotherapeutic agents (53). NF-κB inhibitors were found to sensitize breast cancer cells to doxorubicin (54). Previous studies also showed that phosphorylation and overexpression of NF-κB caused an increase in ER-mediated transcription associated with endocrine resistance. As a positive regulator of Snail in breast cancer cells, simultaneous inhibition of NF-κB by RNA interference resulted in marked increase of cell response to antiestrogen TAM (55). Furthermore, the activation of MAPK and PI3K pathways was also involved in the adaptation of ER-positive breast cancer cells to estrogen deprivation by contributing to ER hypersensitivity and were associated with endocrine resistance (56). High PI3K/Akt activity has been associated with resistance to trastuzumab in HER2-overexpressing cells and primary tumors (57). Additionally, it was revealed that a number of canonical and non-canonical Wnt genes (DKK1, JUN, PORCN, CSNK1A1 and MYC) were significantly increased in the TAM-resistant cells. The Wnt inhibitor, IWP-2, resulted in decreased expression of vimentin and Twist (58). Wnt3 acting as a key mediator in the localization of β-catenin controlled EMT-like transition and activation of EGFR in trastuzumab resistant cells (59).

7. Certain genes involved in EMT and drug resistance in breast cancer

Transglutaminase 2 (TG2), a pro-inflammatory protein implicated in diverse physiological and pathological processes, was reported to induce EMT in MCF-10A cells and confer resistance to doxorubicin as an important downstream mediator of TGF-β (60). Dual specificity phosphatase 4 (DUSP4) is a member of the dual specificity phosphatase family, which inactivates target kinases through dephosphorylating phosphoserine/threonine and phosphor tyrosine residues. Liu *et al* discovered that knockdown of DUSP4 increased the chemosensitivity of MCF-7 and MCF-7/ADR breast cancer cells to doxorubicin, and MCF-7/ADR cells with high levels of DUSP4 had a mesenchymal phenotype (61). Pin1, a peptidyl-prolyl isomerase, was overexpressed in TAM-resistant (TAMR) MCF-7 cells. Pin1 siRNA treatment resulted in decreased Snail transcription and the expression of EMT markers. It was inferred that Pin1 might take part in EMT by affecting PTEN expression and the subsequent PI3-kinase-Akt-dependent GSK-3β inactivation (62). Axl is a transmembrane tyrosine

kinase receptor, activated by either its ligand-growth arrest specific 6 or extracellular domain-mediated dimerization or cross-talk with human EGFR2. It was shown that Axl induced EMT as a upstream factor in normal and immortalized human mammary epithelial cells in an apparent positive feedback loop mechanism and regulate breast cancer stem cells (BCSCs) self-renewal and chemoresistance (63).

8. EMT, CSCs and drug resistance in breast cancer

Cancer stem cells (CSCs), or tumor-initiating cells have been identified as having the ability to form mammosphere, self-renew, exhibiting the $CD44^+/CD24^-$ or high aldehyde dehydrogenase ($ALDH^+$) cell surface maker profile and being associated with invasion, relapse and drug-resistance (64). The stem cells refractory to therapies is mainly because CSCs are known to express increased levels of related members of ABC transporter family and anti-apoptotic proteins (65). Furthermore, these cells are hypothesized to be largely quiescent and slow cycling, which help escape from typical cytotoxic agents (66). BCSCs with high expression of ALDH can also help metabolize cytotoxic drugs (67). Morel *et al* were the first to present evidence linking EMT to BCSCs. It was shown that induction of EMT in transformed mammary epithelial cells generated cells with BCSCs properties (68). This was also corroborated in epithelial breast cancer cells of mouse models (69,70). Circulating tumor cells from metastatic breast cancer patients have shown EMT and tumor stem cell characteristics (71). Basal-like breast cancers, which are enriched for $CD44^+/CD24^-$ cells, are found to exhibit EMT features that might account for their aggressive clinical behavior and metastatic propensities. Moreover, a new subtype called $claudin^{low}$-like was reported recently to display CSC-associated features. In addition, metaplastic tumors which are highly chemoresistant and aggressive are indicated to share molecular similarities with CSCs (72). Both the metaplastic and claudin-low-like tumors are closely related to the EMT core signatures (73). These results support a close connection between EMT and gain of CSC-like properties. Besides, stem-like cells can be generated from differentiated transformed mammary epithelial cells via EMT *in vitro*, suggesting that EMT plays an active role in generating CSCs in human breast tumors. HMLE cells acquired the $CD44^{high}/CD24^{low}$ stem cell profile, after stimulated by TGF-β or in response to constitutive expression of either Twist or Snail (74). The loss of E-cadherin expression that transpires during EMT reinforces these events by permitting the nuclear translocation of β-catenin and its stimulation of CD44 expression (75). Overexpression of Twist in breast cancer cells was demonstrated to promote the generation of a breast cancer stem cell phenotype characterized by the high expression of CD44 and exhibited high efflux of Hoechst 33342 and Rhodamine 123 as a result of increased expression of ABCC1 (MRP1) transporters (76). It was also reported that Twist induced the activation of β-catenin signaling pathway and Akt pathways for the maintenance of the stem cell-like properties associated with EMT (77). Fang *et al* also found that Twist2 not only promoted the EMT program, but also generated cells with stem cell-like properties (78). The ZEB1 transcription factor has been shown to modulate the two stemness genes KLF4 and SOX2 indirectly, via downregulation of miR-200 which are rapidly emerging as master regulators of differentiation by directly targeting the transcriptional factors (ZEB1 and ZEB2/SIP1) to derepress E-cadherin and elicit mesenchymal-epithelial transition (MET), thus leads to the generation of migrating CSCs (79,80). Guo *et al* revealed that Slug could cooperate with SOX9 in orchestrating the stem cell state (81). Collectively, these observations offer unquestionable evidence that EMT inducers are involved in regulating cancer cell stemness.

In addition, HER2-overexpressing breast carcinomas resistance to trastuzumab could also be linked to biology of stem cell-like cells. It was demonstrated that CD44 was overexpressed in trastuzumab resistant JIMT-1 cells and induced HER-2 receptor internalization *in vitro* and *in vivo* (82). Trastuzumab resistance can result from the spontaneous conversion of $HER\text{-}2^+$ cells to a $CD44^+/CD24^-/HER\text{-}2^-$/low phenotype through EMT (83). It was discovered that trastuzumab sensitivity was restricted to the Slug/Snail2-negative subset of luminal/$HER2^+$ cell lines, whereas all of the Slug/Snail2-positive basal/$HER2^+$ cell lines exhibited a primary (inherent) resistance to trastuzumab. Knockdown of Slug could suppress the $CD44^+/CD24^-$/low phenotype which might be responsible for trastuzumab refractoriness in basal/$HER2^+$ JIMT1 cells and sensitize trastuzumab-resistant xenografts to trastuzumab. Quote of a sentence in the chapter: EMT-driving transcriptional repressor Slug/Snail2 appears to be a pivotal gene that induces an enhanced phenotypic plasticity in basal/$HER2^+$ cells, thus allowing them to 'enter' into and 'exit' from trastuzumab-responsive stem cell-like states (84). Thus, EMT may promote drug-resistace via potentiating cell characteristics of CSCs.

9. EMT, microRNAs and drug resistance in breast cancer

MicroRNAs (miRNAs), a class of small cellular RNAs, acting as agents of the RNA interference pathway, can lead to silencing of their cognate target genes, by either cleaving mRNA molecules or inhibiting their translation (85). In this decade, studies have shown that miRNAs regulate EMT through directly targeting families of EMT transcription factors or affecting the integrity of the epithelial architecture during EMT progression (86). miR-200 family which has a striking negative correlation with ZEB could regulate EMT and drug resistance. It was reported that miR-200 expression could reverse resistance to EGFR inhibitor therapy in bladder cancer cells (87). miR-200 cluster was associated with substantial expression of E-cadherin mRNA in breast cancer tissues and low miR-200 expression was associated with pronounced benefits of cyclophosphamide (88). Restoration of miR-200c enhanced chemosensitivity to microtubule-directed agents in MCF-7 and T47D cells (89). In addition, miR-200c was shown to correlate with the acquired resistance of breast cancer cells to doxorubicin by inhibiting Akt signaling through its effects on E-cadherin and PTEN (90). A previous report found that transfection of MDA-MB-231 cells with pre-miR-200b or pre-miR-200c enhanced their sensitivity to doxorubicin. Similarly, reduced miRNA-200b and miR-200c expression contributed to endocrine resistance in breast cancer cells. Accompanied by the increase in miR-200b and miR-200c, ZEB1 expression was decreased and cells appeared more

epithelial in morphology and were sensitized to TAM inhibition (91). It has been proved that miR-125b induced EMT-like molecular alterations, and functioned as a key mediator for Snail-induced stem cell propagation and chemoresistance in breast cancer cells (92,93). A recent study reported EMT was linked to loss of ERα expression, through transcriptional repression of ER by Snail and concomitant translational inhibition of ERα mRNA by miR-221/222 (94). Additionally, miRNA-375 was found downregulated in the TAM-resistant MCF-7 cells, while its re-expression sensitized cells to TAM and reverted EMT-like properties. Metadherin (MTDH) was regarded as the direct target of miRNA-375, with its established relevance in drug resistance and breast cancer metastasis (95).

10. Clinical prognostic of EMT and potential EMT-targeted therapy for breast cancer

The transcriptional factors and the hallmarks of EMT are often related to more malignant type in breast cancer patients. High expression of Slug and Twist has been reported closely correlated with poor prognosis in patients with breast cancer (96,97). Jeong *et al* noted that EMT was significantly related to high histological grade and triple-negative phenotype but not predictive of disease-free survival in patients with breast cancer (98). Since EMT has been established as a mechanism that confers tumor cells with the essential ability for drug resistance, metastasis, and acquired-tumor stem cell traits, inhibition of EMT can be a critical therapeutic strategy for prevention of tumor progression (99). NPI-0052, a protesome inhibitor, has been demonstrated to depress EMT via weakening NF-κB and Snail (100). Shinto *et al* found Ki26894, a TBR-I kinase inhibitor, suppressed the invasiveness and EMT in scirrhous gastric cancer cells (101). Artesunate (an antimalarial agent) has been discovered to induce cell cycle arrest and apoptosis possibly by affecting the hyperactive Wnt pathway and reversing EMT in colorectal cell lines (102). The Src kinase inhibitor dasatinib has been proven to inhibit growth of breast cancer cells with EMT features (103). Cystatin C, a cysteine protease inhibitor has been found to inhibit the acquisition of EMT and invasion stimulated by TGF-β in breast cancer cell by preventing actin cytoskeletal rearrangements and E-cadherin downregulation (104). Chua *et al* developed an EMT inhibition screening assay to identify compounds targeting ALK5, MEK, and SRC as potent inhibitors that can interfere with EGF, HGF, or IGF-1 induced EMT signaling (105).

11. Concluding remarks and future perspectives

EMT is a complex, stepwise phenomenon that occurs during embryonic development and tumor progression, and involves major reprogramming of gene expression that leads to alterations in cell fate and behavior. Clarifying the underlying mechanism linking EMT and drug resistance would likely be useful for devising better targeted therapeutic approaches in combination with conventional therapeutics.

The hallmarks of EMT are loss of the epithelial molecule E-cadherin and gain of mesenchymal markers, such as N-cadherin and vimentin. Loss of E-cadherin expression can lead to loss of contact inhibition, infinite proliferation, de-differentiation, loose intercellular connections, and be susceptibility to shedding in cancer cells, which enhances both invasion and migration of cancer cells (31). N-cadherin is highly expressed in invasive and metastatic human breast cancer cells and correlates with aggressive clinical behavior. The alterations of these genes contribute to endowing cells with higher malignancy. Moreover, an increasing number of direct evidence revealed these genes had close connection with the resistance to therapy (106-108). In addition, the transcriptional factors of EMT such as Snail, Slug and Twist not only elevate the cell invasion and metastasis to escape being killed, but also increase/decrease the essential genes taking part in drug resistance. Certain cytokines and genes play essential roles on both EMT and drug resistance. The signaling pathways of EMT are wide and extremely complex, which constitute main targets for novel drug development. A better understanding of the roles of EMT and CSCs in breast cancer will lead to more effective therapies that will target not only the tumor but also the residual population of cells that are responsible for the relapse and resurgence of the tumor. Further examination of the epigenetic changes such as miRNA will also be an important area of research. All these results suggest that drug combinations using conventional or targeted therapies together with targeting the EMT-related mechanisms need to be considered for winning the battle against drug resistant in cancer cells.

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